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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/923,138	09/04/97	KUCHERLAPATI R	CELL-4.8

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EXAMINER	
BECKERLEG, A	
ART UNIT	**PAPER NUMBER**
1632	20

DATE MAILED: 12/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/923,138	KUCHERLAPATI ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

Continued Prosecution Application

The request filed on 6/13/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/923,138 is acceptable and a CPA has been established. Claims 1-45 are pending in the instant application. Claims 4-45 have been previously withdrawn from prosecution as being drawn to a nonelected invention, based on the restriction requirement in Paper No.8 which applicant timely traversed in Paper No. 11. Claims 1-3 are active in the instant application. An action on the CPA follows.

Applicant's have not presented any claim amendments or any arguments in response to the rejections of record contained in the office action mailed on 3/4/97, paper no. 11, and reiterated in the office action mailed on 5/14/99, paper no. 15. Therefore, for reasons of record, all rejections are maintained as set out in the office action mailed on 3/4/97, paper. no. 11. These rejections are reiterated again below for the applicant's convenience. Please note that in addition to the rejection of record, claims 1-2 have been **newly** rejected for obviousness-type double patenting (see page 10 of the instant office action).

This application should be reviewed for errors. An example of such an error occurs on page 9, line 2, wherein the citation is absent.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to PCT application WO 94/02602 is improper because the claimed mice are only described in the PCT application but are essential to practicing the invention as claimed Incorporation by reference may only occur on an application on which the issue fee has been paid or on an issued US patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification teaches the production of IgM immunoglobulins wherein the human heavy chain constant region is mu and further teaches the production of murine gamma, not human gamma, presumably by trans-switching. The specification does not enable one of skill to make human IgG in the transgenic mouse system. The specification fails to disclose, or enable one of skill to make, the transgene containing the essential nucleotide sequences necessary in the transgene in order for class switching to occur. Therefore, the claims must be limited to IgM having a human variable region, human mu constant region, human kappa chains, and, if IgG, murine gamma constant regions. At the time of the claimed invention was made, 4/27/95, applicants did not have in their possession the transgene capable of undergoing class switching from IgM to IgG. Trans-switching, the switching of the variable region from one constant region to another constant region, was known to occur in the art. For example, a human variable region could switch from the human mu chain constant region to the murine mu constant region of any one of several other isotype gamma constant regions. The declaration by Dr. Cos, of record in U.S. Patent 5,545,806 (application serial no. 07/990,860; Lonberg et al.) and now publicly available, discloses "I am unaware of any reports of successfully cloning intact a Not I fragment containing the region between the human delta and gamma-3 genes or any other restriction fragment containing this region in a YAC vector". Dr. Cox specifically points to applicant's own work (Nature Genetics (1994) Vol. 3, page 88; Nature Genetics (1994) Vol. 7, page 13; and Nature Genetics (1994) Vol. 7, page 162) and declares that cloning of the regions necessary for class switching was not

accomplished by applicants. In view of the foregoing, the specification is not enabling for any constant region other than human mu and the claims must be so limited.

In addition, the claims recite "analogs thereof" and the specification fails to disclose transgenic mice producing only immunoglobulin fragments, presumably the "analogs thereof". The specification discloses mice producing entire immunoglobulin molecules produced from xenomice, the genomes of which are not disclosed herein. The specification does not enable one of skill in the art at the time of filing to produce immunoglobulin fragments in mice containing only intact immunoglobulin genes. The specification fails to disclose how the intact immunoglobulin molecules, once produced *in vivo*, are then manipulated *in vivo* to produce immunoglobulin fragments. Although the claims recite a method to produce an immunoglobulin analog, the xenomice, which are not enabled by the specification for reason disclosed above, apparently do not contain the genes encoding immunoglobulin analogs. Further, the specification fails to enable knockout of the variable region genes per se. Claim 1 specifically recites that the nonhuman animal is incapable of producing endogenous heavy or light chain variable regions. Lacking details of the xenomouse construction, the specification is not enabling for the invention as claimed. Applicants presumably intend that the variable region expression is prevented by knockout of the J region segments, which inhibits expression of the entire chain, not just the variable region.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. The phrase "analog thereof" is vague and unclear since the modification intended is not apparent. While the claims may be interpreted in light of the specification, they are not so limited an the intended metes and bounds of "analog thereof" are indeterminate. Analogs may be nucleotide variants, for example, of the Fab portions or single chain Fvs. Although all are known in the art, it is not known which one or ones applicants are intending to claim. Further, the claims appear to be incomplete since the preamble produces an immunoglobulin while the indented paragraph produces only human immunoglobulin variable regions while the immunoglobulin or analog is recovered in the final step.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 are rejected under 35 U.S.C. 103 as being unpatentable over Surani (USPN 5,545,807) taken with Bruggemann et al. and Krimpenfort (USPN 5,591,669). Surani discloses transgenic mice having inserted into their genomes DNA comprising human Vh, human Dh, human Jh segments and the human mu segment in unrearranged germline configuration such that upon rearrangement of the germline segments, heavy chains containing totally human V regions may be one of the heavy chains produced, the other heavy possibility being a chimeric heavy chain containing a murine variable region. Surani further discloses a method of producing immunoglobulins to a particular antigen comprising administering the antigen to the transgenic mouse and obtaining the immunoglobulin from the cells or body fluids of the mouse. Surani also discloses obtaining immunoglobulins from the B cells of the mouse in addition to producing monoclonal antibodies comprising fusing the B cells with a suitable myeloma fusion partner to produce hybridomas, culturing the hybridomas under suitable conditions for production of monoclonal antibodies and recovering the produced chimeric mouse-human monoclonal antibodies. Surani discloses producing and recovering polyclonal antibodies from the mouse.

Surani additionally discloses insertion of a human antibody gene construct containing a rearranged variable region and a human constant region.

Surani differs from the claims in that the reference fails to disclose a mouse having inactivated endogenous immunoglobulin variable region genes. However, the secondary references, Bruggemann and Krimpenfort, cure this deficiency. Bruggemann discloses the desirability of producing human immunoglobulins in a mouse incapable of expressing endogenous mouse immunoglobulin. Krimpenfort discloses inactivation of endogenous mouse immunoglobulin gene expression by "knocking out" the endogenous genes via homologous recombination. Krimpenfort further discloses that in order to inactivate endogenous immunoglobulin gene expression, the variable region of immunoglobulin genes may be targeted as well as the constant region or the J region (column 8, lines 10-16).

In view of the suggestions by Bruggemann of the desirability of producing human immunoglobulins or chimeric immunoglobulins in mice incapable of expressing endogenous immunoglobulin genes, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the mouse of Surani by knocking out expression of the variable region as taught by Krimpenfort. Bruggemann provides motivation to abolish expression of endogenous immunoglobulin genes while Krimpenfort provides the reasonable expectation of success in being able to abolish the expression of endogenous immunoglobulin genes. Accordingly, the modification of the method of Surani, teaching expression of human immunoglobulin mu chains in transgenic mice, by inactivating endogenous immunoglobulin gene expression as taught by

Krimpenfort in order to produce transgenic mice expressing human immunoglobulins and incapable of expressing endogenous murine immunoglobulins was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention, and therefore, the invention as a whole is *prima facie* obvious.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krimpenfort (USPN 5,591,669) taken with Lonberg (USPN 5,545,608). Krimpenfort discloses making transgenic mice having the endogenous immunoglobulin genes inactivated by targeting constructs and therefore incapable of expressing endogenous immunoglobulins. Krimpenfort differs from the claims in that the reference fails to disclose further addition of a transgene encoding human immunoglobulin genes. However, the secondary reference, Lonberg, cures the deficiency. Lonberg discloses a method for producing human immunoglobulins to a specific antigen from a transgenic mouse comprising administering the antigen and collecting the produced immunoglobulins. Both Krimpenfort and Lonberg disclose transgenic mice having the endogenous immunoglobulin heavy chain and light chain gene loci inactivated and therefore mice incapable of producing endogenous immunoglobulins (column 28, lines 34-and continued in column 29). Lonberg discloses that rearranged or unrearranged V segments may be isolated with or without flanking sequences (column 25, lines 60-64) and further discloses production of polyclonal antibodies. Lonberg discloses the motivation for making transgenic mice expressing human

immunoglobulin genes and having the murine endogenous immunoglobulin loci inactivated and further discloses mice making human heavy chains in an endogenous immunoglobulin gene knock-out background. See table 9, column 80. Krimpenfort is cited to disclose the knockout technique and for the teachings that such was old and well known in the art at the time the claimed invention was made. Both Krimpenfort and Lonberg provide the reasonable expectation of success in obtaining inactivation of endogenous immunoglobulin gene expression in transgenic mice, while Lonberg discloses both the knockout condition and the insertion of human immunoglobulin genes into the murine genome for purposes of making human antibodies to human antigens.

Accordingly, the modification of the method of Krimpenfort by adding a transgene encoding human immunoglobulins as taught by Lonberg was within the ordinary skill in the art the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention, and therefore, the invention as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2 are **newly** rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-12 of U.S. Patent No. 6,150,584 (11/21/00), hereafter referred to as '584. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. The applicant claims methods of producing an immunoglobulin with a fully human variable region comprising administering an antigen to a nonhuman animal characterized by being substantially incapable of producing endogenous heavy or light chain variable regions, but capable of producing human immunoglobulin variable regions, and recovering said immunoglobulin. The applicant further claims said method wherein the polyclonal immunoglobulin is recovered. The '584 patent claims methods of producing fully human IgG antibody comprising administering an antigen to a transgenic mouse whose genome comprises inactivated endogenous immunoglobulin heavy chain loci such that expression of endogenous immunoglobulin is prevented and DNA fragments of human chromosome 14 comprising human heavy chain gene segments and human chromosome 2 comprising human light chain gene segments such that the resulting mice can produce fully human antibodies. The '584 methods represents a species of the broader methods claimed in the instant application in that the '584 claims limit the non-human animal to a mouse and recite specific genomic modification such that the resulting mouse substantialy incapable of producing

endogenous heavy or light chain variable regions, but capable of producing human immunoglobulin variable regions. As such, the species claims of the '584 patent render the genus obvious. In regards to the limitation to the recovery of polyclonal antibodies, it is noted that while the '584 claims recite the broader term "antibodies", the specification of the '584 patent clearly teaches that the antibodies to be recovered are in fact polyclonal. Thus, the '584 claims encompass and render obvious the limitation of claim 2 in the instant application to polyclonal antibody.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg